## REMARKS

Informalities

The application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Sequences and SEQ ID NO's are provided in paper and computer readable form for peptides "FTLEISR" and "LTLKLSR." No new matter has been added.

Per Examiner, the first line of the specification was amended to reflect the relationship between the instant application and Provisional Patent Application 60/165,424 filed on November 14, 1999.

The drawing in the application is objected to by the Draftsperson under 37 CFR 1.84, per the Notice of Draftsperson's Review (Form PTO 948), dated May 13, 2002. Per Examiner's request, proposed formal drawing is submitted herewith along with a marked up version showing the changes. Please substitute the enclosed formal drawing for the originally submitted drawing. No new matter is contained in the formal drawing.

The abstract of the disclosure is objected to because SEQ ID NO is required for an amino acid sequence. The SEQ ID NO has been added as specified.

The disclosure is objected to because of the requirement for SEQ ID NO for TAT-PASS peptide. The SEQ ID NO has been added as specified.

Claims 6 and 13 are objected to because the claims fail to comply with the requirements of 37 CFR 1.821(d), which required SED ID NO.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. Namely, it was suggested that the applicant amend the specification to provide support for peptides "FLTEISR" and "LTLKLSR" recited in the original claim 13.

Claim 12 is objected to because the recitation of "hsc 73" has no support in the specification as filed.

Status of the claims

Claims 1-12 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification is non-enabling as for what is recited in the original claims. Claims 1-12

and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 1-13 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

Claims 1-8, 10-13 and 15-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Davids *et al.* ("Davids") (J Immunology 163: 3842-50, Oct 1999). Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Boland *at al.* ("Boland") (J Biol Chem 271(30): 18032-44; 1996).

Claims 1,3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davids or Boland in view of Gardner *et al* ("Gardner") (J Biol Chem 268(34): 25940-47, 1993), Schubert *et al* ("Schubert") (European J Neuroscience 9: 770-777, 1997) or Ohashi et al ("Ohashi") (Virchows Arch 428(1): 37-46, 1996). Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davids or Boland in view of U.S. Pat No. 5,276,059 (January 1994).

Amendments to the claims

Applicants have added new claims 21-22. Claims 21 and 22 are nearly identical to the Examiner's description of the enablement of the original specification. Support for newly added claim 21 can be found in the specification at, for example, section *Binding Protein Inhibition Detail*, pages 7-9.

Support for newly added claim 22 can be found in the specification at, for example, section *In vivo Aggregation Inhibition Detail*, pages 10-14.

Claims 1-12 and 17-20 are rejected under 35 U.S.C. 112, first paragraph. The Applicants have amended these claims, incorporating nearly the identical language proposed by the Examiner. In light of the amendments to claims 1-7, 10-13, and 17-20, the §112, first paragraph rejection pertaining to these claims is obviated. Support for the new recitation of these claims can be found in the original specification in sections *Binding*

*Protein Inhibition Detail* and *In vivo Aggregation Inhibition Detail.*

Claims 1-13 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. These claims have been amended by the Applicant to incorporate the Examiner's suggestions. The §112, second paragraph rejection pertaining to these claims is obviated.

Davids is not prior art under section 102(a).

Claims 1-8, 10-13 and 15-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Davids. In light of the swear back affidavit attached hereto, Applicant submits that the Davids reference is now obviated. Specifically, inventor Fred J. Stevens, pursuant to 37 C.F.R. 1.131 (attached herewith), swears behind the publication date of the Davids reference. In fact, the inventor declares that the instant application was reduced to practice at least as early as January 12, 1999. Attached to the affidavit is an invention report from Argonne National Laboratory, dated January 12, 1999. The 1.131 affidavit in its present form effectively swears behind the publication date of the cited Davids reference. As such, the Applicants submit that the Davids reference does not act as prior art against the instant application.

Claim 1 is allowable over Boland.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Boland. As now amended, claim 1 recites (a) identifying SMA or LEN mutation in the amino acid sequence of said protein that leads to fibril formation; (b) substituting each mutation into SMA or LEN to identify the residues of a peptide that contribute to fibril formation; (c) synthesizing peptides spanning most of the light chain variable region that interacts with an endoplasmic reticulum chaperone selected from the group consisting of BiP, Hsp 70, and combinations thereof; (d) determining the $V_L$-derived peptides for their ability to prevent fibril formation in vitro wherein the peptides are selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKLSR (SEQ ID NO: 13), and combinations thereof; and (e) preventing fibril formation by inserting the said peptide into the complimentary region of the light chain variable

domain. As specified in amended claim 1, the insertion peptides are derived from a homolog of the protein being prevented from aggregating. Boland does not derive its insertion moiety from a homolog of the protein being prevented from aggregating. Rather, Boland discloses using a serine protease inhibitor to *mediate* cell surface binding, internalization, and degradation of soluble amyloid-β peptide (see, e.g., Boland, abstract) (emphasis added). The serine protease inhibitor disclosed in Boland is not derived from the aggregating protein and does not insert itself into the amyloid protein, thus preventing fibril formation. Hence, claim 1 is allowable over Boland.

Claims 1, 3, and 9 are allowable.

Claims 1, 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davids or Boland in view of Gardner, Schubert, or Ohashi. For reasons already discussed, Applicants submit that the Davids reference cannot be used to form an obviousness rejection. Furthermore, for reasons stated supra, any rejection based on Boland are obviated.

Gardner, Schubert, and Ohashi, in separately or in combination, do not teach what is now recited in amended claim 1, namely the minimizing of aggregation of amyloid forming proteins by the specified method (*supra*). First, Gardner does not deal with aggregation at all, but rather with protein degradation. Gardner discloses the use of a serine protease, different from a serpin–serine protease *inhibitor* (emphasis added) (. (protease normally degrades proteins while a protease inhibitor inhibits the actions of a protease). The disclosed serine protease mediates the degradation of immunogolobulin light chains and does not deal with preventing aggregation of amyloid forming proteins by insertion of small peptides into the proteins (see, e.g., Gardner, abstract).

Schubert is an observation that the antiprotease activities of serpins may be responsible for inhibiting the toxicity of amyloid peptides. Similarly to Boland, Schubert does not mention the use of small peptides that insert into homologous regions of amyloid-forming proteins, thus preventing fibril formation.

Ohashi is a discussion of an inflammation phenomenon, namely, the involvement

Davids and Boland has been traversed, *supra*. Second, the '059 patent does not teach a method of minimizing the aggregation of proteins via insertion of peptides. Instead, the '059 reference discloses the use of non-biological chemicals such as Congo Red or salts to treat amyloidogenic diseases (see, e.g., column 2, lines 15-20 and 61-64. Hence, claim 1 is allowable over the cited prior art. Because claim 9 depends on claim 1, it is also allowable.

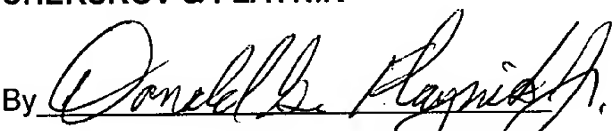
**CONCLUSION**

Applicants submit that in light of the foregoing amendments and remarks thereto, the application is deemed in order for allowance.

An earnest attempt has been made hereby to respond to the §102, §103 and §112 rejections contained in the July 29, 2002 official action. Applicants submit that the instant amendment places the application in condition for allowance. If the Examiner feels that a telephonic interview will expedite allowance of the Application, she is respectfully urged to contact the undersigned. Reconsideration and allowance of claims 1-13,15-20, and allowance of new claims 21-22 is hereby solicited.

Respectfully submitted,

**CHERSKOV & FLAYNIK**

By 

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A FIBRIL-BLOCKING PEPTIDE, A METHOD
FOR PREVENTING FIBRIL FORMATION

## BACKGROUND OF THE INVENTION

This Application is based on Provisional Patent Application 60/165/424 filed on November 14, 1999.

1. Field of the Invention

This invention relates to a fibril-preventing peptide and a method for preventing the formation of fibrils and more particularly, this invention relates to a peptide and a method for preventing the formation of solid protein structures and disease associated therewith.

2. Background of the Invention

"Conformational diseases," share a common etiology whereby proteins fold irregularly to produce structural flaws. These flaws result in the proteins unnaturally aggregating and thereafter precipitating as fibrils from their solvents. Such solvents include blood, urine, water, lymph, cerebrospinal fluid, and other physiological fluids. Diseases such as sickle cell anemia, amyloid light chain disease, senile systemic amyloidosis, Alzheimer's, and prion encephalopathies including kuru and "mad cow" disease or BSE, are the result of protein conformation anomalies.

The immunoglobulin light chain (LC) is normally a soluble, secreted protein, but some light

Peptides derived from the VL sequence, including known BiP-binding peptides, were tested for their ability to prevent SMA fibril formation. Eighteen synthetic peptides spanning most of the $V_L$ sequence were tested. Among the eighteen synthetic peptides were FTLEISR (SEQ ID NO: 12) and LTLKLSR (SEQ ID NO: 13). Of them, PKLLIYWA (44-51) exhibited partial inhibition and the overlapping peptides TDFTLTI (amino acids 69-75) and FTLTISS (71-77) markedly inhibited the aggregation. The peptide FTLKISR, a 71-77 sequence common to a number of $V_L$ germline genes inhibited as well as FTLTISS and also inhibited fibril assembly of the peptide λ6 $V_L$ protein. Specific structural features of the sequence 71-77 are important for inhibiting aggregation. Peptides in which Phe71 or Ile75 were replaced by Leu were effective inhibitors. However, a peptide with the same amino acids as in the native sequence but in a scrambled order did not inhibit, nor did any of the peptides with Phe71, Leu73 or Ile75 in FTLKISR replaced by Ala. Placement of a Pro in a middle of the peptide also abolished its inhibitory capacity, suggesting that the extended conformation of the peptide is essential.

The inventors have found that the same features of the peptide required for inhibiting aggregation are also necessary for this peptide's binding to BiP. The ability of both BiP and its target $V_L$ peptide to inhibit aggregation therefore suggests that under aggregation-promoting conditions, the loop containing the TDFTLTISS peptide in SMA is not anchored properly in the body of the V domain. The peptide inhibits fibril formation through interactions between its hydrophobic patch on partially unfolded SMA that mimics the BiP binding site.

The readiness with which SMA adopts fibrillogenic conformation as compared to LEN must be due to the minimal sequence differences between the two.

In addition to suggesting a molecular mechanism for light chain amyloidosis, the inventors' results also imply that many somatic mutants of immunoglobulin are involved in such aggregation. Only one (or a few) destabilizing mutation(s) is required to convert a soluble protein to an aggregate prone variation. Further, even if such a mutant does not aggregate spontaneously, it may be induced to form fibrils by the presence of another aggregating light chain, a potentially common *in vivo* event. Identification of these specific structural features should facilitate future development of rational strategies for drug discovery across the spectrum of amyloid disease.

Taken together, these experiments show that the fate of misfolded, amyloidogenic LC was altered by increased interactions with Hsp70 family chaperones on either side of the ER membrane: more SMA was retained in the ER, less was aggregated and more of it remained in a soluble state, whether in the lumen of the ER or in the cytosol. Since the majority of SMA at steady state is in the dislocated, cytosolic pool, BiP would be expected to have less of an effect than Hsp70 when the total cellular protein is analyzed and this is indeed what we observed.

The inventors also found that An Hsp70-binding peptide derived from the LC sequence inhibits SMA aggregation in vivo. To optimize delivery of the peptide to all cellular compartments, it was synthesized with the 11-mer sequence from the HIV TAT protein at the N-terminus (Gius et al., 1999). This TAT peptide permits the transduction of denatured proteins across cell membranes rapidly and efficiently in an energy- and receptor-independent fashion. In addition to the test peptide, TAT-TISS, another TAT-fusion was employed as a specificity control. This peptide, TAT-PASS (SEQ ID NO: 10), contains four amino acid substitutions and does not inhibit fibril formation *in vitro*. SMA transfected cells were incubated overnight in the presence of increasing concentrations of ALLN and 50 μM of each peptide. In the range of 1-10 μg/ml ALLN, there was a progressive increase in the amount of SMA found in the soluble fraction on a per cell basis. Inclusion of the TAT-TISS peptide dramatically reduced the amount of SMA recovered at all ALLN concentrations tested. In contrast, the TAT-PASS (SEQ ID NO: 10) peptide had no effect. Incubation of the same blots with anti-raf antibody demonstrated that equal cell equivalents were loaded across the gel.

The inventors also determined the effect of different concentrations of peptide on SMA following treatment with 10 μg/ml ALLN. The TAT-TISS peptide decreased the yield of SMA in the insoluble fractions much more than in the detergent soluble fractions. The magnitude of the decrease was from 4 to 10-fold (n=3), in a peptide concentration-dependent fashion, whereas the TAT-PASS (SEQ ID NO: 10) peptide had only a marginal effect even at the highest concentration used. As observed with co-expression of Hsp70, upon addition of the TAT-TISS peptide, the ubiquitinated forms of SMA were diminished. This indicated that they were being maintained in a soluble form long enough to be kept off the aggregation pathway and were degraded by the proteasome.

Lastly, the inventors determined that the decrease in steady state level of SMA in the presence

of TAT-TISS peptide correlated with a decrease in the frequency of aggresome formation, by scoring anti-kappa stained cells. Roughly 30% of untreated cells exhibited aggresomes and this number increased to about 65% upon addition of ALLN. Transduction of TAT-TISS decreased the number of aggresomes by more than half, to 25%, about the same as in untreated cells, whereas addition of TAT-PASS (SEQ ID NO: 10) peptide had no significant effect. Hence, the large decrease in insoluble SMA observed in the presence of TAT-TISS peptide coincides with a drop in aggresome formation.

In summary, the inventors have found that peptides which mimic the structure of amyloid-forming proteins are suitable agents in inhibiting fibril formation. Insertion of the peptides into a particular groove typically occupied by an adjacent fibril unit interrupts fibril assembly and thus prevents fibril formation.

When amyloidogenic light chain (LC) fails to fold properly it is dislocated out of the endoplasmic rediculum to the cytosol where two linked coping mechanisms are present. While much of the expelled light chain is degraded by proteasomes, another fraction of the light chain aggregates. The inventors found that the introduction of a specific peptide into the cell inhibits aggregation and increases the efficiency of LC degradation.

The presence of a non-releasing BiP mutant ( or high levels of wild type BiP) traps SMA molecules in the ER lumen that would otherwise be disloacted to the cytosol for aggregation.

Alternatively, once dislocated, interaction of SMA with cytosolic Hsp 70 improves the efficiency of aggregation. Over-expression of Hsp 70 decreased the insoluble and ubiquitin-tagged pools of SMA that accumulate in the presence of proteasome inhibitors. In the absence of proteasome inhibitors, however, the level of endogenous Hsp 70 was sufficient to support degradation of most SMA light chains. The inventors have identified a kinetic competition between degradation and aggregation: when there is sufficient Hsp 70 present to keep SMA soluble, more of it gets degraded, but if the level of Hsp 70 is inadequate, then more SMA aggregates. SMA is a type of proteasomal substrate whose degradation is improved by chaperon interactions.

FIG. 4 depicts the inventor's competitive inhibition model. SMA fails to progress along a productive folding pathway and hence both of its domains remain in the reduced state *in vivo*. The presence of the highly unstable κ4 protein is detected by BiP, presumably during or soon after its

translocation across the ER membrane. Binding to BiP prevents SMA aggregation in the lumen and facilitates its dislocation back to the cytosol. Once there, binding to Hsp70 (or related chaperones) serves to maintain SMA in a degradation-competent state, so that it can be ubiquitinated and rapidly targeted to proteasomes. At the same time, Hsp70 inhibits the tendency of SMA to aggregate in the cytosol, thus regulating the balance between degradation and aggregation.

The inability to fold exposes (at least) the two major peptides in each of the two β sheets of the V domain that are good sites for binding of Hsp70 family chaperones. Continued exposure of these sites enables associations first with BiP (within the ER) and then with Hsp70 (in the cytosol). The FTLTISS peptide which is effective in reducing intracellular aggregation has the sequence of one of these two major sites, and importantly, the same features that are required for its anti-aggregation activity are necessary for its Hsp70 binding activity.

The inventors envisage the peptide to interact with the same amino acids in the hydrophobic core of the V domain normally occupied in the folded molecule by the endogenous FTLTISS peptide. In this way, the peptide acts as a surrogate chaperone, inhibiting aggregation and promoting degradation. This provides a new avenue for treatment modalities using rationally designed peptides to suppress aggregation.

While the invention has been described through the embodiments disclosed herein, it should be noted that the embodiments are not intended to limit the scope of the following claims.

1. (Amended) A method for minimizing the aggregation tendencies of an amyloid forming protein, the method comprising:

a) identifying [a first amino acid sequence of the protein that is replaced by a second amino acid sequence during physiological conditions, and] SMA or LEN mutation in the amino acid sequence of said protein that leads to fibril formation;

b) [preventing the replacement by juxtaposing a peptide to the first amino acid sequence] substituting each mutation into SMA or LEN to identify the residues of a peptide that contribute to fibril formation;

c) synthesizing peptides spanning most of the light chain variable region that interacts with an endoplasmic reticulum chaperone selected from the group consisting of BiP, Hsp 70, and combinations thereof;

d) determining the $V_L$-derived peptides for their ability to prevent fibril formation in vitro wherein the peptides are selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKLSR (SEQ ID NO: 13) and combinations thereof; and

e) preventing fibril formation by inserting the said peptide into the complimentary region of the light chain variable domain.

2. (Amended) The method as recited in claim 1 wherein the method is conducted in [*vivo*] a cell.

3. (Amended) The method as recited in claim 1 wherein the protein is [a human protein selected from the group consisting of] human kappa-4 light chain variable domain or a greek key fold protein selected from the group consisting of antibody constant domains, transthyretin, beta-2 microglobulin, serine protease inhibitors, and crystalline.

4. (Amended) The method as recited in claim 3 wherein the peptide [has] is an amino acid sequence identical to an amino acid sequence in a region of the light chain variable domain.

5. (Amended) The method as recited in claim 3 wherein the peptide is inserted between residue position numbers 60 and 83 of the [protein] human kappa-IV light chain.

6. (Amended) The method as recited in claim 3 wherein the peptide [has] is the amino acid sequence $Phe_{71}$-$Thr_{72}$-$Leu_{73}$-$Thr_{74}$-$Ile_{75}$-$Ser_{76}$-$Ser_{77}$ (SEQ ID NO: 1) and wherein the subscripts denote the positions of the amino acids in the domain.

7. (Amended) The method as recited in claim 1 wherein the peptide is inserted when the amyloid forming protein is partially unfolded.

10. (Amended) The method as recited in claim 9 wherein the peptide is inserted at a hairpin anchorage point in the [greek key fold] human kappa-IV protein and its derivatives selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKLSR (SEQ ID NO: 13), and combinations thereof.

12. (Amended) The method as recited in claim 1 wherein the peptide is an endoplasmic reticulum chaperone selected from the group consisting of hsp70 [hsc73,] and BiP.

13. (Twice Amended) The method as recited in claim 1 wherein the peptide interacts with endoplasmic reticulum chaperone, the peptide selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 11), and LTLKLSR (SEQ ID NO: 12).

17. (Amended) A method for preventing fibril assembly of human kappa-IV immunoglobulin, the method comprising:

a) identifying [a region of a first aggregating protein moiety that normally interacts with a second moiety to form the assembly; and] the mutations LEN and SMA in the amino acid sequences of human kappa-IV immunoglobulin;

b) [juxtaposing a binding protein to the first moiety] substituting each SMA mutation into LEN to identify the residues of the peptide that contribute to fibril formation;

c) synthesizing peptides selected form the group consisting of those peptides spanning most of the variable region of the light chain that interacts with an endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70; and

d) determining the $V_L$-derived peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKLSR (SEQ ID NO: 13), and combinations thereof for their ability to prevent fibril formation.

18. (Amended) The method as recited in claim 17 wherein the [first and second aggregating proteins are] protein involved in fibril assembly is [immunoglobulin] human kappa-IV immunoglobulin light chains.

19. (Amended)The method as recited in claim 17 wherein the binding protein [hybridizes] binds with the region.

20. (Amended)The method as recited in claim 17 wherein the binding protein is an amino acid sequence that is [complementary to] the same as the amino acid sequence of the region.

21. (New) Method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain *in vitro*, the method comprising:

a) identifying the LEN and SMA mutation in the amino acid sequence of said protein;

b) substituting each SMA mutation into LEN to identify the residues of a peptide that contributes to fibril formation;

c) synthesizing peptides spanning most of the variable region of the light chain that interacts with an endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70;

d) determining the $V_L$-derived peptides for their ability to prevent SMA fibril formation in vitro wherein the peptides are selected from the group consisting of

TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKLSR (SEQ ID NO: 13), and combinations thereof.

22. (New) A method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain protein in a cell, the method comprising:

a) identifying the LEN and SMA mutation in the amino acid sequence of said protein;

b) substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril aggregation;

c) synthesizing peptides spanning most of the variable region of the light chain that interacts with an endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70;

d) expressing SMA or LEN in COS cells;

e) treating said cells with said peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKLSR (SEQ ID NO: 13), and combinations thereof; and

f) determining the $V_L$-derived peptides for their ability to prevent SMA fibril aggregation in said cell by western blotting or immunoflourosence.

ABSTRACT

A method for minimizing the aggregation tendencies of an amyloid forming protein is provided comprising identifying a portion of the protein that is critical to amyloid formation; and inserting a peptide at the portion. The invention also provides a peptide for insertion in an intact human kappa-IV light chain variable domain, the peptide comprising the following amino acid sequence $Phe_{71}$-$Thr_{72}$-$Leu_{73}$-$Thr_{74}$ -$Ile_{75}$-$Ser_{76}$-$Ser_{77}$ (SEQ ID NO. 1) wherein the subscript numbers are the residue location points in the domain. A method for preventing amyloid formation in human kappa-IV light chain variable domain is also provided, the method comprising inserting the peptide $Phe_{71}$-$Thr_{72}$-$Leu_{73}$-$Thr_{74}$ -$Ile_{75}$-$Ser_{76}$-$Ser_{77}$ (SEQ ID NO. 1) into the domain, wherein the subscript numbers indicate the residue location on the domain.